UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,029	12/16/2005	Sally-Anne Stephenson	2381.0010000/MAC	9023

26111 7590 05/26/2009

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
HALVORSON, MARK	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
05/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,029	STEPHENSON, SALLY-ANNE	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-12,14-19 and 21-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12,14-19 and 21-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Claims 1-5, 7-12, 14-19 and 21-45 are pending and under examination.

35 USC § 112 1st paragraph rejection maintained

The rejection of claims 1-5, 7-12, 14-19 for failing to comply with the enablement requirement is withdrawn in view of Applicants Declaration of March 13, 2009.

NEW REJECTIONS:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-12, 14-19 and 21-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the cancerous growth of a colon or breast cancer cell that expresses EphB4 comprising contacting the cell with an antibody that binds an EphB4 epitope located within residues 200-400 of EphB4II, inducing the death of a cancer cell and treating or preventing cancer in a subject comprising contacting the cells with an antibody to an epitope on EphB4, does not reasonably provide enablement for a method for inhibiting the

cancerous growth of a mammalian cell that expresses EphB4 comprising contacting the cell with an antibody that binds an EphB4 epitope located within residues 200-400 of EphB4, inducing the death of a cancer cell and treating cancer in a subject comprising contacting the cells with an antibody to an epitope on EphB4, wherein the EphB4 epitope located within residues 200 – 400 of EphB4 (SEQ ID NO:1) but wherein the amino acid at residue 226 is Asn (N) instead of Asp (D) or preventing cancer in a mammalian subject comprising administering an antibody to an epitope located within residues 200-400 of EphB4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method for inhibiting the proliferation of a cancer cell, inducing the death of a cancer cell and treating or preventing cancer in a subject comprising contacting the cells with an antibody to an epitope on EphB4. The claims read on a method of preventing or treating cancer in a subject.

The specification discloses that EphB4 expression was upregulated on colon and breast cancer cells. (Example 1) The specification also discloses that polyclonal antibodies to EphB4 induced cell death in breast and colon cancer cell lines. (Example 3). The specification further discloses that cell death by the polyclonal antibodies is inhibited by specific EphB4peptides. (Fig 14). The specification does not disclose any in vivo studies on the treatment of cancer with antibodies to EphB4.

Applicant's Declaration filed on March 13, 2009 discloses that a monoclonal antibody (AB-1) that binds to an epitope within residues 220-230 of SEQ ID NO:1 is as effective as doxorubicin in inhibiting tumor growth in a animal model for breast cancer in vivo. (paragraphs 11, 12, Figs 2 and 4). There was little difference between the effect of doxorubicin and the vehicle control on tumor growth. (Figs 1 and 2).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide examples or guidance for inhibiting the cancerous growth of a mammalian cell, other than a colon or breast cancer cell, that expresses EphB4 comprising contacting the cell with an antibody that binds an EphB4 epitope. The specification only demonstrates inhibiting the cancerous growth of a colon

or breast cancer cell that expresses EphB4 comprising contacting the cell with an antibody that binds an EphB4 epitope. The specification does not provide a nexus between inhibiting the cancerous growth of any mammalian cell that expresses EphB4 and the administration of an antibody that binds an EphB4 epitope to a patient.

MPEP 2164.03 states that

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention.

MPEP 2164.03 further states that

> The "predictability or lack thereof" in the art refers to the ability of one skilled in the art toextrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. …
>
> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. In re Vickers, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); In re Cook, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir.

1991). This is because it is not obvious from the disclosure of one species, what other species will work.

The claims of the instant application are not enabled because the teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention. Thus, the claims are not enabled for on a method of treating cancer in a subject. In particular, it is well known that the art of anti-cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042, cited previously) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.).

In addition, the treatment of disease with antibodies in vivo is generally unpredictable. White et al (Annu Rev Med 52:125-145, 2001, cited previously) discloses that despite monoclonal antibody testing since the mid-1900's only in the past three years have some monoclonal antibodies provided sufficient efficacy as therapeutic agents (see Abstract). According to White et al, "The use of monoclonal antibodies for the treatment of carcinoma and hematologic malignancies is an evolving field". (see Conclusion). White et al discloses that numerous obstacles must be overcome for successful immunotherapy. These include choice of target antigen, immunogenicity of the antibodies, length of half-life and ability to recruit effector functions and antibody manufacturing.

Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004, cited previously) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized

anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art and the specification recognize that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification and the in vivo date using an animal model for breast cancer that it would be more likely than not that the claimed antibody or variations of the antibody claimed could be effectively used for the treatment of any cancer. Although the tumor which was used to stimulate production of the claimed antibody clearly expresses the antigen, it is clear as set forth above, that it cannot be predicted, even when antigen is expressed that the claimed antibody would be effective for treating any cancer.

It is apparent from the art that the treatment of cancer is unpredictable. As recently as 2007, Noren et al (Cancer Res, 2007, 67:3994-3997, cited previously) stated that it is unknown if EphB4 therapeutic will be effective in the treatment of cancer. (page 3007, 2nd column). Noren et al disclose that the Eph receptors are present on most tissues. (page 3994, 1st column). Upregulated expression of EphB4 has been reported in types of cancer (page 3994, 1st column). Noren et al also states that the role of EphB4 in cancer is unknown and that more research is needed to resolve the many confusing and controversial issues. (page 3997, 2nd column).

All of this underscores the criticality of providing workable examples. However, there is only one *in vivo* working examples for the treatment of breast cancer comprising administering an antibody to EphB4. The specification and Declaration provides insufficient guidance with regard to these issues which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, undue experimentation would be required to practice the claimed invention.

Because of the known unpredictability of the art, in the absence of experimental evidence in appropriate animal models, with data commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the claimed antibodies would be effective a method for inhibiting the cancerous growth of a mammalian cell that expresses EphB4 comprising contacting the cell with an antibody that binds an EphB4 based on the ability of the antibody to EphB4 to induce cell death of a breast cancer cell line and a colon cancer cell line in vitro and the ability of the antibody to EphB4 to reduce tumor growth in an in vivo model of breast cancer.

Furthermore, one cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide examples or guidance for preventing cancer in a subject comprising contacting the cells with an antibody to an epitope on EphB4. The specification only demonstrates treating cancer in a subject comprising contacting the cells with an antibody to an epitope on EphB4.. The specification does not provide a nexus between the prevention of cancer in a subject and the administration of an antibody to an epitope on EphB4.

With regards to the prevention of cancer in a mammal comprising administering an antibody, the specification does not disclose sufficient guidance or objective evidence that such antibodies would predictably prevent the formation of cancer cells in a mammal. The prevention of cancer, let alone the prevention of cancer with an antibody, is highly unpredictable. The majority of studies suggest that the essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in *advance* of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. Further, such studies require the appropriate experimental models for analyzing chemo- or immunoprevention. For example, Granziero *et al.* (Eur. J. Immunol. 1999, 29:1127-1138, cited previously) teach that many models are not suitable for testing immunotherapeutic approaches intended to cure cancer. They suggest that the optimal model (prostate cancer, in their case) would have spontaneous tumor development in its natural location (1st column, page 1128) wherein disease progression would closely resemble the progression of the particular type of cancer. Hence, depending on the

type of model employed one could establish a reasonable link between antecedent drug and subsequent knowledge of the prevention of the disease. Further, reasonable guidance with respect to correlating agents that prevent cancer may depend upon quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. For example, Byers, T. (CA Journal, Vol. 49, No. 6, Nov/Dec. 1999, cited previously) teaches that randomized controlled trials are commonly regarded as the definitive study for proving causality (1st col., p.358), and that in controlled trials the random assignment of subjects to the intervention eliminates the problems of dietary recalls and controls the effects of both known and unknown confounding factors. Further, Byers suggests that chemo-preventitive trials be designed "long-term" such that testing occurs over many years (2nd col., p. 359). The specification is devoid of any models or experimental analysis that reasonably suggests that the claimed method would predictably prevent the formation of tumors in a mammal. This, combined with the state of the art of preventing cancer, suggests that undue experimentation would be required to practice the invention as broadly claimed.

In addition, one cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide examples or guidance for inhibiting the cancerous growth of a mammalian cell, that expresses EphB4 comprising contacting the cell with an antibody that binds an EphB4 epitope, wherein the EphB4 epitope located within residues 200 – 400 of EphB4 (SEQ ID NO:1) but wherein the amino acid at residue 226 is Asn (N) instead of Asp (D). The specification only demonstrates inhibiting the cancerous growth of a colon or breast cancer cell that expresses EphB4 comprising contacting the cell with an antibody that binds an EphB4 epitope wherein the EphB4 epitope located within residues 200 – 400 of EphB4 (SEQ ID NO:1). The specification does not provide a nexus between inhibiting the cancerous growth of any mammalian cell that expresses EphB4 and the administration of an antibody that binds an EphB4 epitope wherein the EphB4 epitope

located within residues 200 – 400 of EphB4 (SEQ ID NO:1) but wherein the amino acid at residue 226 is Asn (N) instead of Asp (D).

The specification discloses that antibodies to EphB4, that bind to an epitope within residues 220-230 of SEQ ID NO:1, induced cell death in breast and colon cancer cell lines (Examples 3 and 6). Applicant's Declaration, filed on March 13, 2009, discloses that a monoclonal antibody (AB-1) that binds to an epitope within residues 220-230 of SEQ ID NO:1inhibits tumor growth in a animal model for breast cancer in vivo (paragraphs 11, 12, Figs 2 and 4). The specification does not disclose that an antibody that binds an EphB4 epitope wherein the EphB4 epitope located within residues 200 – 400 of EphB4 (SEQ ID NO:1) but wherein the amino acid at residue 226 is Asn (N) instead of Asp (D) inhibits tumor growth either in vitro or in vivo.

The state of the prior art is such that it is well established in the art that the substitution of one amino acid of a polypeptide with another amino acid changes the immunoreactivity of that polypeptide. For example, Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci., 1980, 77:3211-3214) disclose that dissociation of immunoreactivity from other activities when constructing analogs and demonstrated that the deletion of one amino acid abolished or reduced immunoreactivity (see entire document).

The art teaches that a substitution of one amino acid abrogates the ability of an antibody to bind to its epitope. Thus, many antibodies that bind to an EphB4 epitope located within residues 220 – 230 of EphB4 (SEQ ID NO:1 would not bind to an EphB4 epitope located within residues 200 – 400 of EphB4 (SEQ ID NO:1) but wherein the amino acid at residue 226 is Asn (N) instead of Asp (D). As such, one of skill in the art would not know how to use the claimed antibody. There if no disclosure in the specification on the use of an antibody that binds to an EphB4 epitope located within residues 200 – 400 of EphB4 (SEQ ID NO:1) but wherein the amino acid at residue 226 is Asn (N) instead of Asp (D).. The specification provides insufficient evidence or nexus that would lead the skilled artisan to predict the ability of using antibodies that

bind to a polypeptide with 95% sequence identity to the polypeptide of SEQ ID NO:4 or antibodies that bind to a polypeptide with 95% sequence identity to the polypeptide of SEQ ID NO:6.

Given the disclosure of the specification and the teaching in the art that indicates the abrogation of an antibody to bind its ligand by a single amino acid substitution, one skilled in the art could not predictably use an antibody that binds an EphB4 epitope wherein the EphB4 epitope located within residues 200 – 400 of EphB4 (SEQ ID NO:1) but wherein the amino acid at residue 226 is Asn (N) instead of Asp (D).

Therefore, in view of the breadth of the claims, lack of guidance in the specification, the absence of working examples, and the state of the art, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Applicant asserts that Dr. Stephenson's Declaration establishes that the specification is enabled for the claimed invention and that the information contained in the disclosure of the specification is sufficient to inform those skilled in the relevant art how to both make and use the claimed invention in a manner that satisfies the requirements of 35 U.S.C. § 1 12, first paragraph for enablement. Applicant argue that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, In re Wands. Applicant argues that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. In re Fisher. Applicant argues that the specification disclosure, which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Applicant argues that it is incumbent upon the Office, whenever a

rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Applicant also argues that 35 U.S.C. § 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. Applicant argues that it is not necessary that every permutation within a generally operably invention be effective in order to an inventor to obtain a generic claim, provided that that effect is sufficiently demonstrated to characterize a generic invention.

Applicant's arguments have been considered but are not persuasive. In response to Applicant's argument's that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. However, as previously stated the treatment of cancer with antibodies is very unpredictable. The disclosure that an antibody to EphB4 inhibits tumor growth in an animal model for breast cancer and the ability of an antibody to cause cell death in breast and colon cancer cell line in vitro is not sufficient to enable the claims of the present invention, as broadly written.

MPEP 2164.08(b) states that

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Although, typically, inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of

> operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. In re Angstadt, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.

Applicants have only demonstrated that a few cancer cell lines overexpress EphB4 in addition to the disclosure that an antibody to EphB4 inhibits tumor growth in an animal model for breast cancer in vivo and the ability of an antibody to cause cell death in breast and colon cancer cell line in vitro. Furthermore, as recently as 2007, Noren et al stated that it is unknown if EphB4 therapeutic will be effective in the treatment of cancer. Noren et al also states that the role of EphB4 in cancer is unknown and that more research is needed to resolve the many confusing and controversial issues.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art.' In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The “amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

In response to Applicant argument that it is not necessary that every permutation within a generally operably invention be effective in order to an inventor to obtain a generic claim, provided that that effect is sufficiently demonstrated to characterize a generic invention, one of ordinary skill in the art would not conclude that the treatment of

one type of cancer in vivo with an antibody would sufficiently enable claims reading on significant numbers of inoperative embodiments and when the specification does not clearly identify the operative embodiments and where undue experimentation would be involved in determining those embodiments that are operative.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Claims 40 is drawn to a method for inhibiting the cancerous growth of a mammalian cell that expresses EphB4 comprising contacting the cell with an antibody that binds an EphB4 epitope located within residues 200-400 of EphB4II, inducing the death of a cancer cell and treating or preventing cancer in a subject comprising contacting the cells with an antibody to an epitope on EphB4, wherein the amino acid sequence of said cell's EphB4 comprises that of amino acids 16-987 of SEQ ID NO:1. Applicant points to Figure 8 and SEQ ID NO:1 as well as page 6 line 5 and page 9 line 4 for support. However, none of these citation lend support for a sequence of amino acids consisting of amino acids 16-987 of SEQ ID NO:1.

Summary

Claims 1-5, 7-12, 14-19 and 21 stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone

number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Mark Halvorson/
Examiner, Art Unit 1642